

Disease Modifying Antirheumatic drugs



ILOS

At the end of the lecture the students should:

- Know the pathogenesis of rheumatoid joint damage
- Emphasize the rationale for early treatment of RA
- Define and classify **DMARDs**
- Compare and contrast the advantages and disadvantages of **NSAIDs, Steroids and DMARDs** in treatment of RA
- Know some examples of drugs related to DMARDs.
- Explore the pharmacokinetic and pharmacodynamic aspects of the selected DMARDs
- Describe the mechanism of action, specific clinical uses, adverse effects of individual drugs.

EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

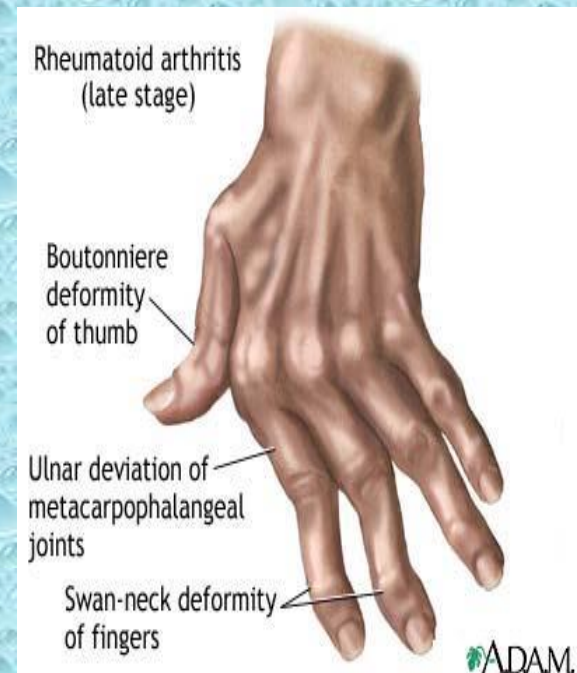
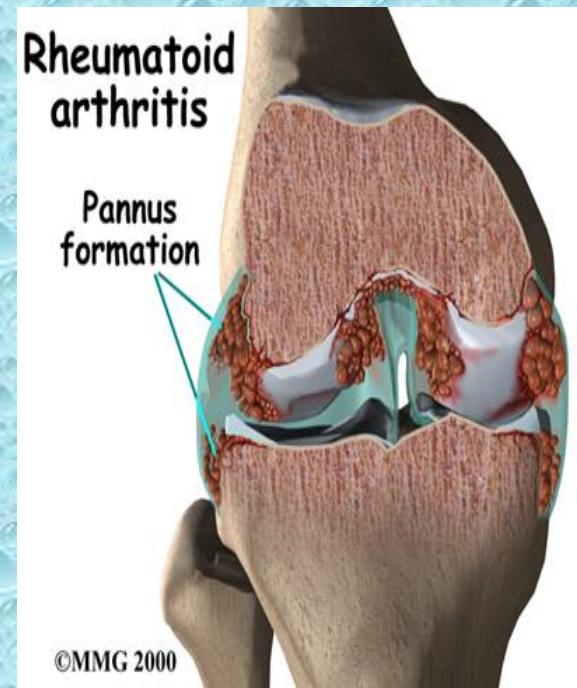
Affects 1-2 % of the adult population

Is more common among women than in men (2-3 times)

Usually appears between ages 25 and 40 years

The incidence also increases with age, peaking between the 4th and 6th decades

Causes pain, disability and loss of function



RHEUMATOID ARTHRITIS

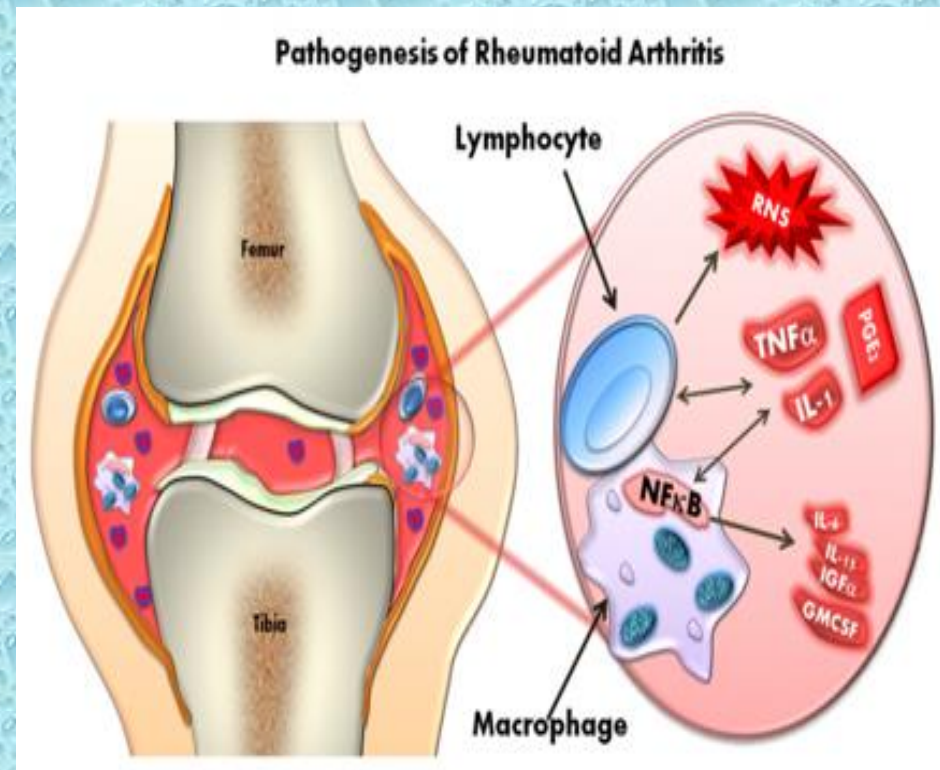
RA is a chronic **autoimmune** disorder in which the normal immune response is directed against an individual's own tissue leading to:-

Decline in functional status

Work disability &
socioeconomic costs

Systemic complications

Co-morbidity &
Increased mortality



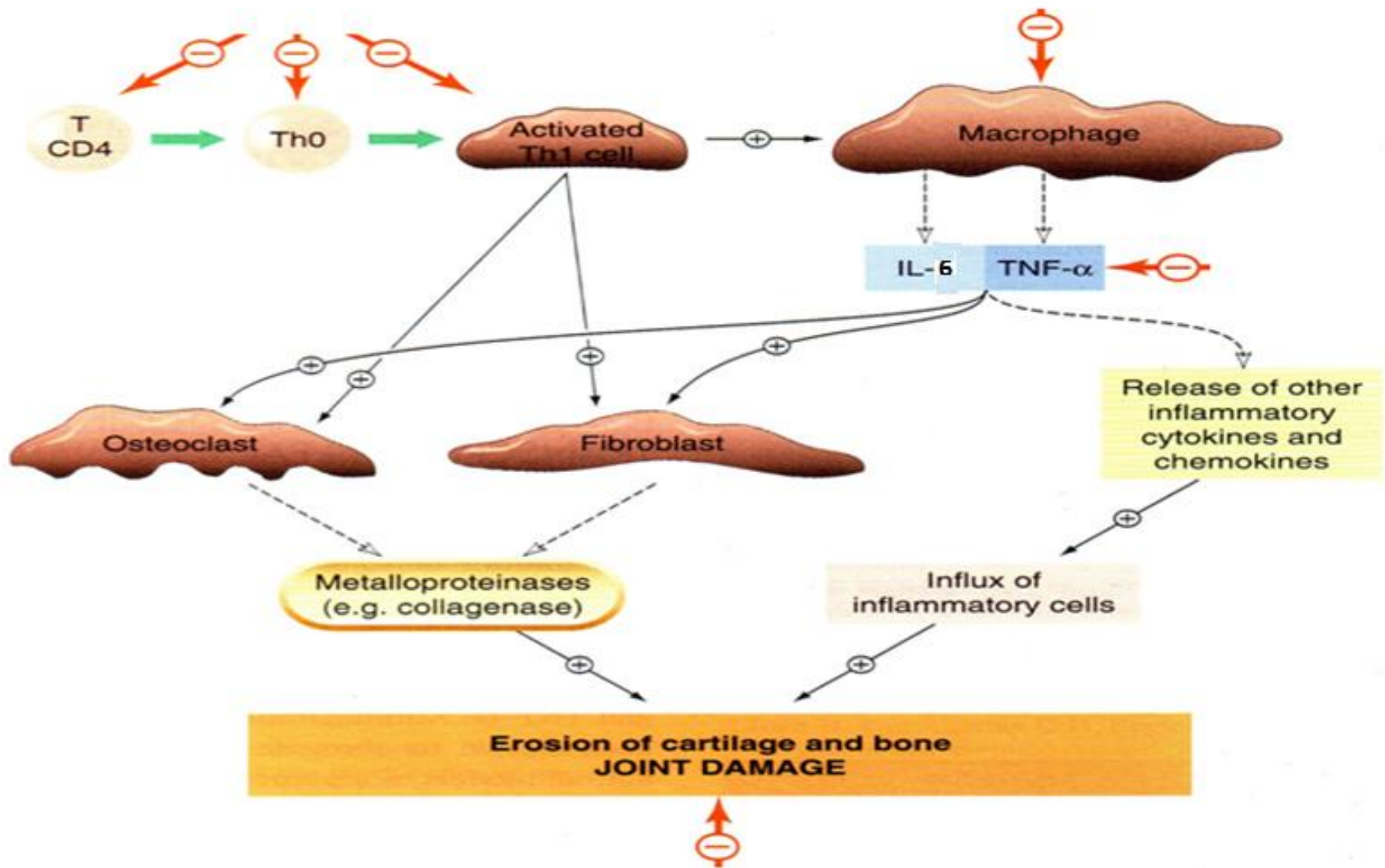
Synovial inflammation and hyperplasia ,
autoantibody production (rheumatoid
factor), cartilage and bone destruction
("deformity")



Anaemia
Weight loss
Osteoporosis
Amyloidosis
Renal, cardiovascular
and neurological
complications

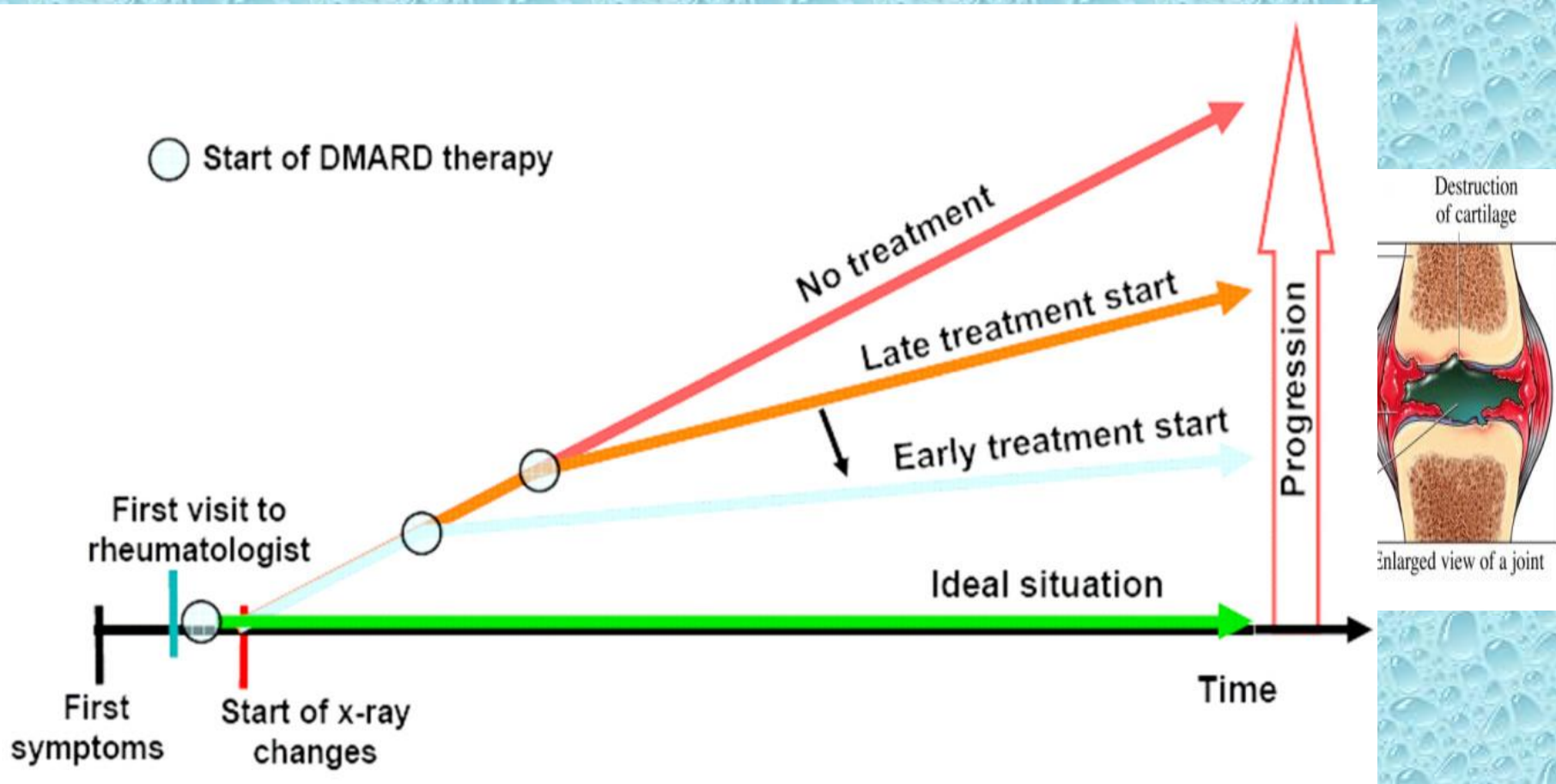
RA damages joints and may be systemic

PATHOGENESIS



Mechanism of action:
not clearly known

RATIONAL FOR EARLY TREATMENT



Early and aggressive treatment may have long-term benefits

CLASSIFICATION

Drugs for Rheumatoid Arthritis

DMARDs

NSAIDs

Glucocorticoids

Classical

Biologic

GLUCOCORTICOIDS

Anti-inflammatory drugs with an **intermediate rate** of action (slower than NSAIDs but faster than other DMARDs).

May be administered in low to moderate doses to **achieve rapid disease control before the onset of fully effective DMARD therapy**

Reserved for temporary control of severe exacerbations and long-term use in patients with **severe disease not controlled by other agents.**

Corticosteroids are too toxic for routine chronic use

NSAIDS

Rapid onset of action

Used in acute cases to **relief inflammation & pain**

Provide partial relief of pain and stiffness

Do not slow the progression of the disease

Chronic use should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.



Comparison between NSAIDs & DMARDs

DMARDs

- Slow onset of action
- Arrest progression of the disease
- Prevent formation of new deformity
- Used in chronic cases when deformity is existing

NSAIDs

- Rapid onset of action
- No effect
- Can not stop formation of new deformity
- Used in acute cases to relief inflammation & pain

CLASSIFICATION OF DMARDs

DMARDs

act on the immune system to slow the progression of RA



Biologic

Infliximab

Tocilizumab

Classical

Methotrexate

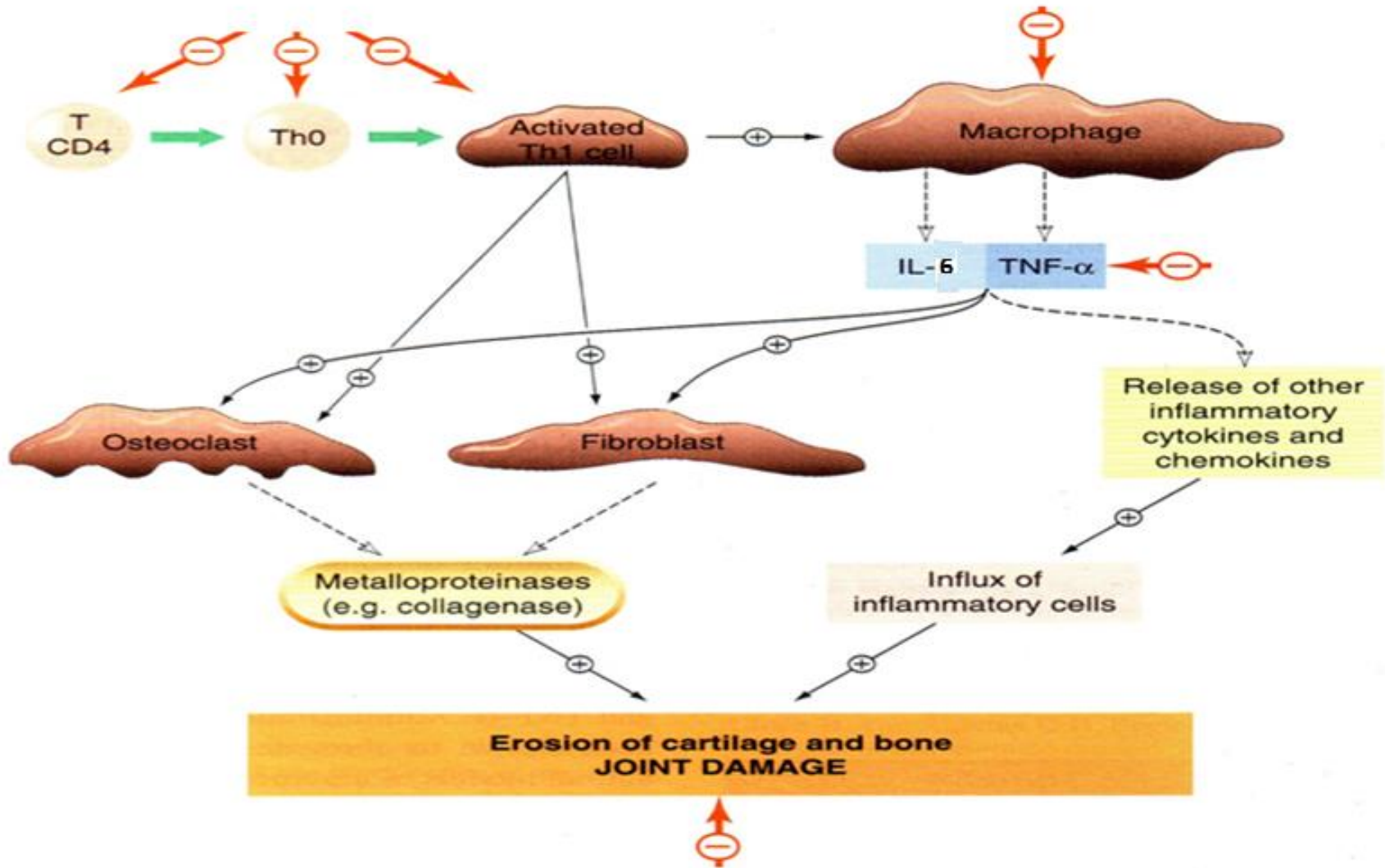
Hydroxychloroquine

Rheumatoid Arthritis

Bone erosion



DMARDs-MOA



Mechanism of action:
not clearly known

GENERAL FEATURES

Used when the disease is progressing & causing deformities

Can not repair the existing damage, but prevent further deformity

Have no analgesic effects

Their effects take from **6 weeks up to 6 months** to be evident



METHOTREXATE

“Gold standard” for DMARD therapy & is the first-line DMARD for treating RA and is used in 50–70% of patients

Active in RA at much **lower doses** than those needed in cancer chemotherapy

MECHANISM

Inhibits dihydrofolate reductase

Reduces thymidine & purine synthesis

But at the dosages used for the treatment of RA, methotrexate has been shown **to stimulate adenosine release from cells**, producing an anti-inflammatory effect.

Inhibition of polymorphonuclear chemotaxis

Inhibition of T-Cells (cell-mediated immune reactions)

METHOTREXATE

PHARMACOKINETICS

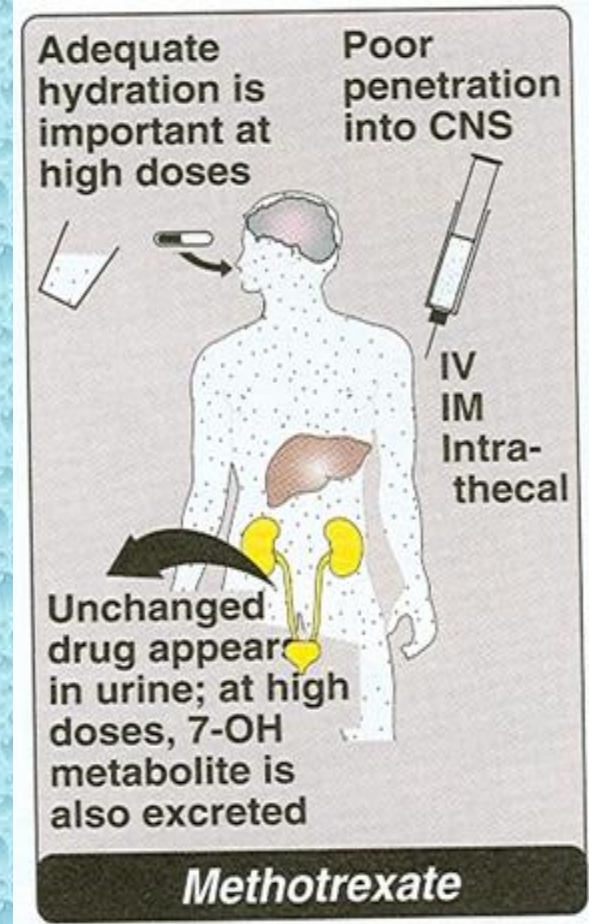
Approximately 70% absorbed after oral administration

Metabolized to a less active hydroxylated product

Half-life is usually only 6–9 hours

Excreted principally in the urine, but up to 30% may be excreted in bile.

Given 7.5 – 30 mg weekly



ADRS

Bone marrow suppression

Dyspepsia, Mucosal ulcers

Hepatotoxicity

Pneumonitis

Teratogenicity

Leukopenia, anemia, stomatitis, GI ulcerations, and alopecia are probably the result of inhibiting cellular proliferation

Folic acid reduces GI & bone marrow effects

Monitoring: -Full blood count, ALT, Creatinine



HYDROXYCHLOROQUINE

MECHANISM

Stabilization of lysosomal enzyme activity

Trapping free radicals

Suppression of T lymphocyte cells
response to mitogens

Inhibition of leukocyte chemotaxis



HYDROXYCHLOROQUINE

PHARMACOKINETICS

Rapidly absorbed and 50% protein-bound

Extensively tissue-bound, particularly in melanin-containing tissues such as the eyes

Elimination half-life of up to 45 days

Highly concentrated within cells → increases intracellular pH

HYDROXYCHLOROQUINE

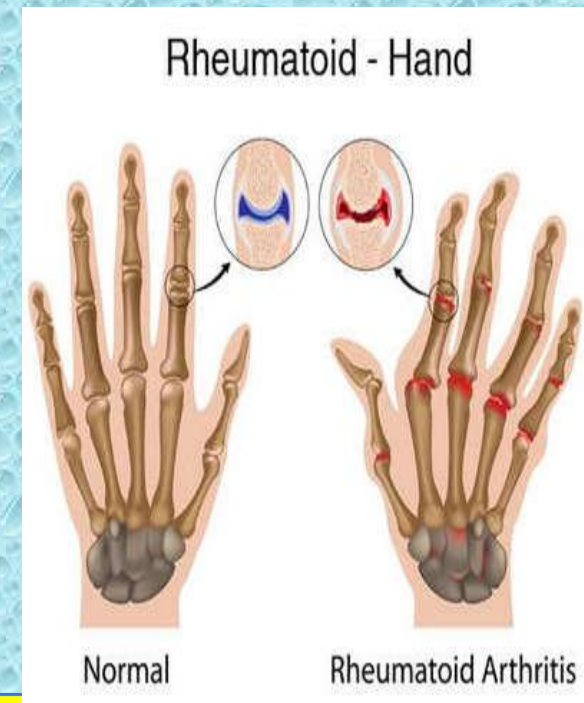
CLINICAL USES

Has not been shown to delay radiographic progression of disease

Generally used for treatment of **early, mild disease** or as adjunctive therapy in combination with other **DMARDs**.

Used in **increasing methotrexate efficacy**

6 month response, mild anti-rheumatic effect



ADRS

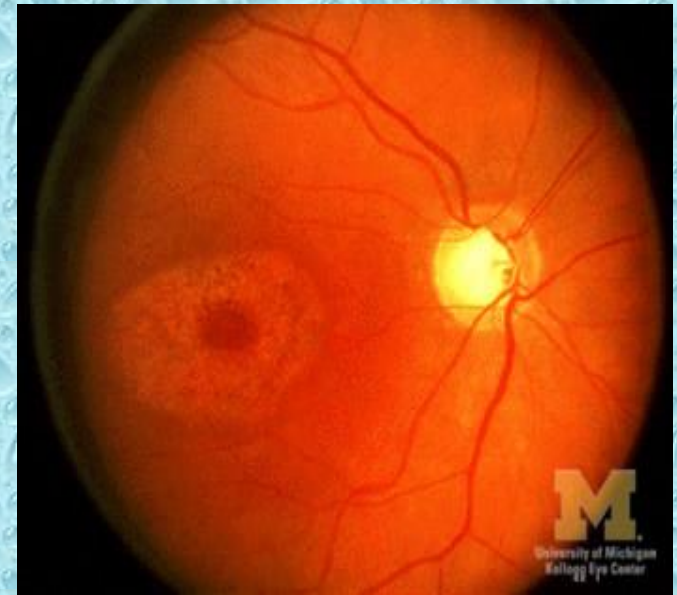
Least toxic, no blood tests is required

Nausea & vomiting

Corneal deposits

Irreversible retinal damage

Ophthalmologic evaluation every 6 months



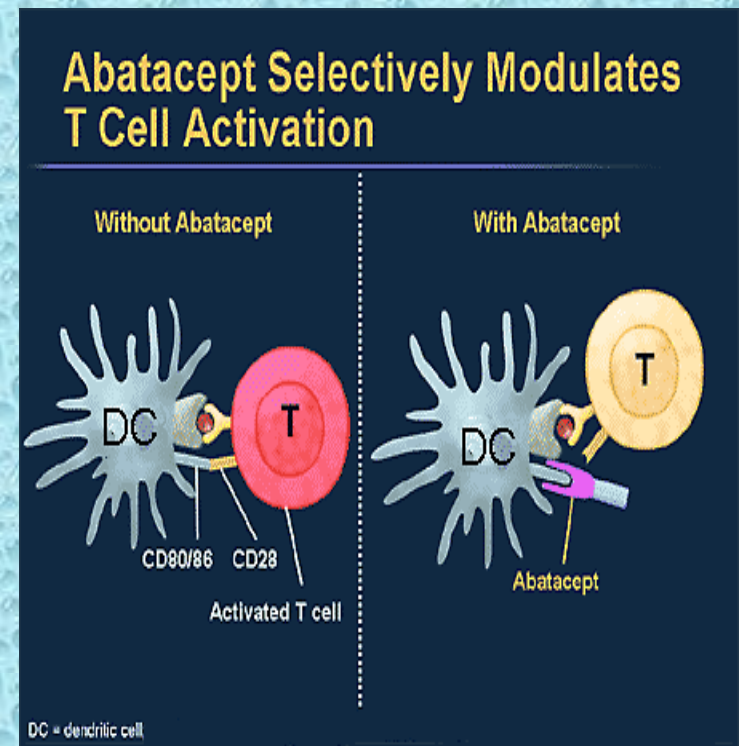
BIOLOGIC DISEASE MODIFIER

Genetically engineered drugs that are used to modify imbalances of the immune system in autoimmune diseases.

Some of these agents block, or modify the activity of **selected cells in the immune system**

Others work by blocking **cytokines**, that send signals between those cells

They are expensive



BIOLOGIC DISEASE MODIFIER

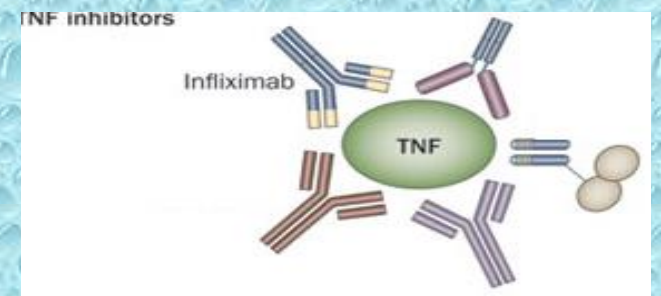
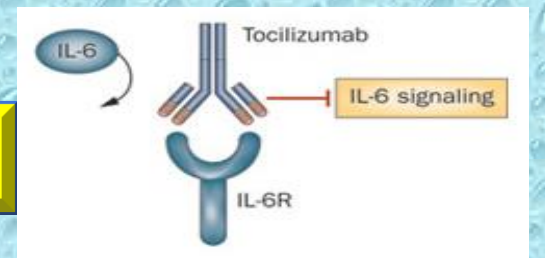
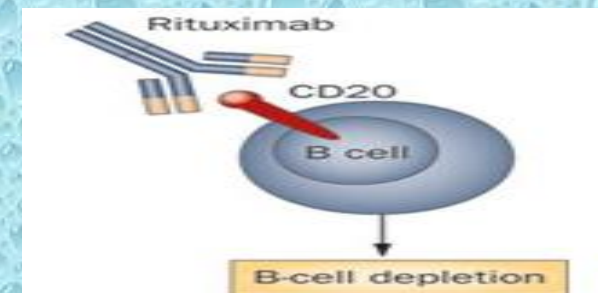
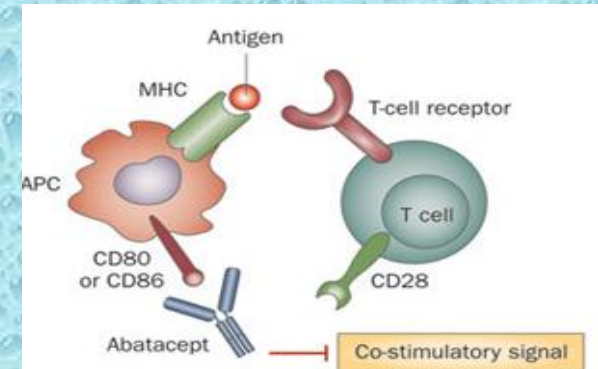
CLASSIFICATION

❖ T-cell modulating drug (Abatacept)

❖ B-cell cytotoxic agent (Rituximab)

❖ Anti-IL-6 receptor antibody (Tocilizumab)

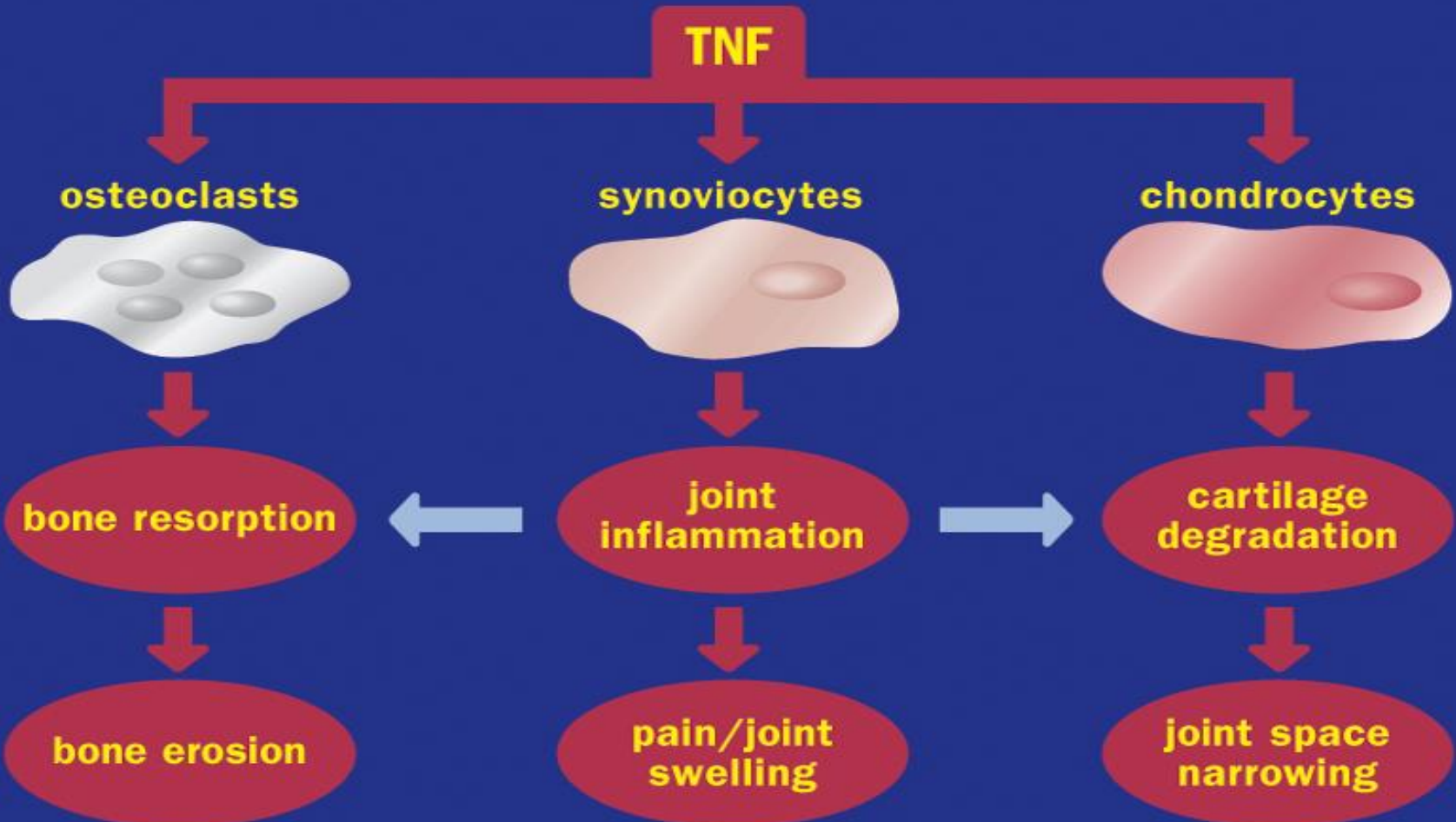
❖ TNF- blocking agents (Infliximab)



TNF α BLOCKING AGENTS

ROLE OF TNF ON JOINT DESTRUCTION

Destructive effects of TNF



TNF α BLOCKING AGENTS

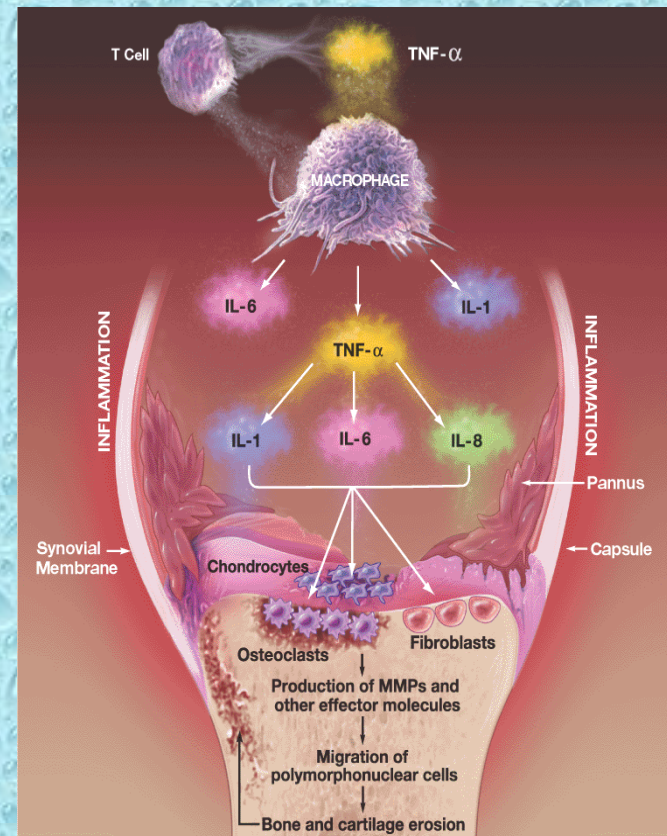
INFLIXIMAB

A chimeric IgG₁ monoclonal antibody (25% mouse, 75% human)

MECHANISM

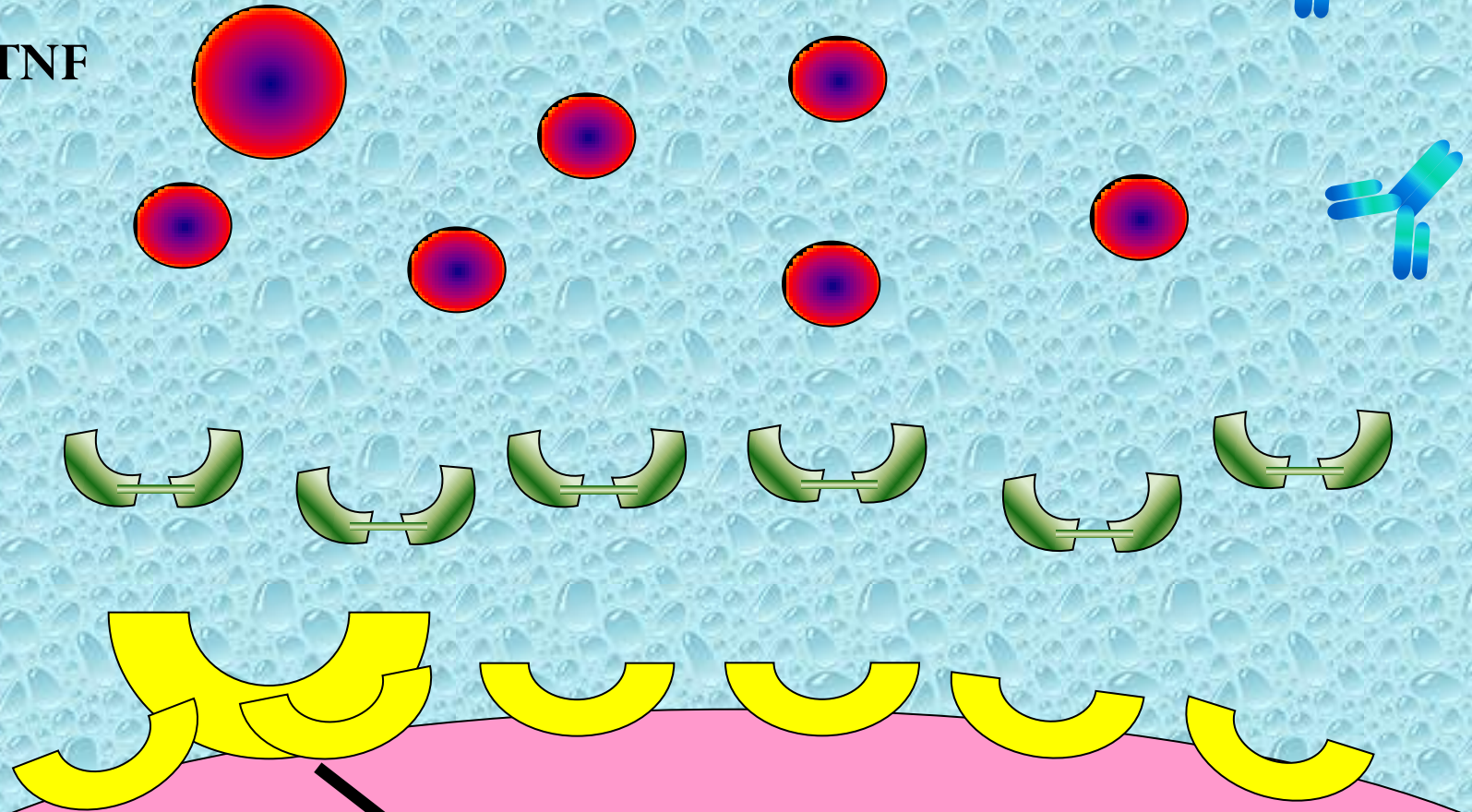
It complexes with soluble TNF- α (and possibly membrane-bound TNF- α) and prevents its interaction with the cell surface receptors

This results in down-regulation of macrophage and T-cell function.



Monoclonal Antibody directed against TNF-
Engender TNF Receptor TNF Receptor
alpha: Infliximab (Remicade®), Adalimumab
(Humira®), Etanercept
(Enbrel®), Humira®

TNF



SIGNAL

INFLIXIMAB

PHARMACOKINETICS

Given as an **intravenous infusion** with “induction” at 0, 2, and 6 weeks and maintenance every 8 weeks thereafter,

Terminal half-life is 9–12 days

After intermittent administration elicits human antichimeric antibodies in up to 62% of patients

Concurrent therapy with **methotrexate** decreases the prevalence of human antichimeric antibodies



INFLIXIMAB

CLINICAL USES

Infliximab is approved for use in RA, Ankylosing spondylitis, Crohn's disease, ulcerative colitis,

It could be combined with methotrexate, hydroxychloroquine and other non biological DMARDs

INFLIXIMAB

ADRS

Upper respiratory tract infections

Activation of latent tuberculosis

Infusion site reaction

Headache

Cough

Increase the risk of skin cancers—
including melanoma

TOCILIZUMAB

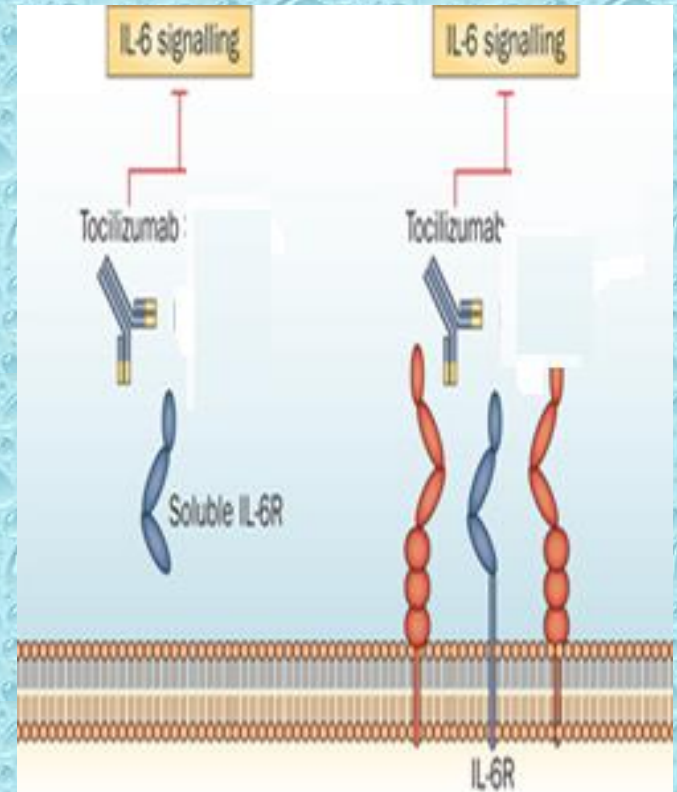
IL-6 is a proinflammatory cytokine implicated in the pathogenesis of RA,

With detrimental effects on both joint inflammation and cartilage damage

Tocilizumab binds to membrane IL-6 receptors, **blocking the activity of IL-6** in mediating signals that affect cytokine production, osteoclast activation

Half-life is dose-dependent

Given as monthly **IV**



TOCILIZUMAB

CLINICAL USES

Used as monotherapy in adult with rheumatoid arthritis or in children over 2 years with systemic juvenile arthritis

In combination with **methotrexate** or other non biologic anti-rheumatic drugs in patients with active rheumatoid arthritis not responding to TNF blockers or other biologic drugs



TOCILIZUMAB

ADRS

Infusion reactions

Serious infections (bacterial, tuberculosis ,fungal)

Increase in cholesterol level

Neutropenia, and thrombocytopenia
(reversible upon stopping the drug)

Decrease in WBCs

Increase in liver enzymes

Blood tests will be used monthly for increase in cholesterol, liver enzymes & decrease in WBCs

TOCILIZUMAB

DRUG INTERACTIONS

IL-6 inhibits CYP450

Tocilizumab restores the activity of the enzyme (essential for the metabolism of some drugs such as cyclosporine, warfarin).



BEST WISHES

The image features a central orange horizontal bar with the text "BEST WISHES" in a white, serif font. The top and bottom sections of the image are filled with a pattern of light blue water droplets of various sizes, creating a textured, bubbly appearance.